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A low dose of subcutaneous nicotine improves information processing in non-smokers

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Abstract. Many studies have found that cigarette smoking or nicotine improves mental functioning in abstinent smokers. An unresolved issue is whether this improvement is due primarily to a direct facilitation of performance or to relief of the impairment caused by nicotine withdrawal. We evaluated the performance of 12 non-smokers before and twice (15 and 45 min) after a subcutaneous injection of 0.8 mg nicotine, 0.8 ml saline, and a control no treatment, on a choice reaction time (RT) task. Each treatment was given on a separate day; the control day was given on the first session. The order of nicotine and saline was balanced between subjects, and injections were given double-blind. The RT task manipulated stimulus and response processing. These manipulations consisted of two levels of stimulus complexity and two levels of response complexity, resulting in four task conditions. These manipulations along with latency measures of the event-related potential were used to identify the components of processing that mediated nicotine's effects on performance. During each active drug session blood nicotine levels, cardiovascular, and subjective responses were measured before and after each of the three tests (pre-drug, 15 min and 45 min post-drug). For the information processing measures only the comparisons of the pre- and 15-min post-test showed significant drug effects. Nicotine compared to saline significantly increased the number of responses at the fast end of the RT distribution. However, there were no changes in accuracy. Nicotine also speeded mean RT compared with saline or the control day, but the effects were only significant for the control-nicotine comparison. There was an interaction between effects of nicotine and the task variables, such that nicotine speeded P3 latency in the hardest task condition, while slowing it in the other task conditions. Nicotine significantly increased heart rate, which lasted for the entire session. Blood nicotine levels were lower than expected from a preliminary study in smokers and may have been responsible for the smaller than expected mean RT effects. These findings suggest that even a low dose of nicotine directly affects attention or stimulus processing components of information processing. This study also illustrates the importance of assessing both multiple components of information processing and nicotine levels when examining the effects of nicotine on cognition.

Key words: Blood nicotine – N100 – Nicotine – Non-smokers – P300 – Reaction time – Speed accuracy – Subcutaneous

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In general smokers report that smoking helps them to think and to concentrate, but also to relax or to calm themselves, particularly in stressful situations (McKennell 1970; Russell et al. 1974). It has become clear in recent years that tobacco withdrawal symptoms can evoke distressing changes in mood and behavior. Such withdrawal symptoms may discourage smokers from trying to quit or cause abstinent smokers to relapse (Hughes et al. 1990). It is now widely accepted that the psychopharmacological effects of nicotine are responsible for the addiction (Surgeon General's Report 1988). However, the mechanisms that mediate the psychological effects of smoking remain to be established. The actions of nicotine on the central nervous system are of particular interest because they reinforce smoking behavior. Tobacco dependence may be maintained by a combination of the positive, or rewarding, effects of nicotine on cognitive function (Wesnes and Warburton 1984; Warburton et al. 1986), and the avoidance of the negative, or aversive, effects of withdrawal symptoms (Hughes et al. 1990).

Many studies have found that cigarette smoking or administration of nicotine improves mental functioning in abstinent smokers (see US Department of Health and Human Services 1988 for a comprehensive review). However, this body of research has serious methodological limitations. First, the improvement in performance after

smoking could be due to a direct facilitation of cognitive performance by nicotine or to relief of the impairment caused by nicotine withdrawal (Hughes 1991). Second, while the role of nicotine in determining the effects of smoking on performance is generally inferred, it has rarely been directly assessed. Neither actual nicotine intake, nor nicotine blood levels (reflecting nicotine intake) have been measured. Most studies have experimentally manipulated the type of cigarette, comparing cigarettes with low and high nicotine delivery, or varied the number of cigarettes smoked. Neither of these measures accounts for inter-individual variability in smoking behavior and nicotine absorption (Benowitz and Jacob 1984; Feyerabend et al. 1985).

Because the possibility of nicotine withdrawal effects cannot be excluded in smokers, it is necessary to study the effects of nicotine in non-smokers. Nicotine administered by oral tablets produced improvements on the Stroop task (Wesnes and Warburton 1978) and a visual vigilance task (Wesnes et al. 1983) in smokers and non-smokers, and also produced improvements on a rapid information processing task in non-smokers (Wesnes and Warburton 1984). In a further study with non-smokers, however, nicotine tablets were not found to improve performance on either the rapid information processing task or the Stroop test, although the drug did reverse the negative effects of scopolamine on these two tasks (Wesnes and Revell 1984). The oral route of nicotine administration is not optimal to simulate the pharmacokinetics of nicotine absorbed during smoking because of slow absorption through the buccal mucosa, and the reinforcing properties of nicotine may be due to its ability to quickly stimulate the nicotinic receptors in the brain (Benowitz et al. 1990; Le Houezec and Benowitz 1991).

A third limitation is that the effects of nicotine have focused on performance; little attention has been paid to the neurocognitive processes that mediate performance (Le Houezec and Benowitz 1991). Edwards et al. (1985), for example, reported that nicotine speeded RT and the P3 latency of the event-related potential (ERP). Changes in P3 latency are largely under the control of stimulus variables (Van der Molen et al. 1991), while response variables generally affect RT without changing P3 latency (Callaway 1984; Magliero et al. 1984; see Naylor et al. 1993 for a review). The results of Edwards et al. thus suggest that nicotine improves performance by acting on stimulus variables. This interpretation is consistent with the findings showing that anticholinergic drugs such as scopolamine slow P3 latency and RT (Callaway et al. 1985; Brandeis et al. 1992). By contrast, amphetamine speeds RT but has only a small effect on P3, suggesting that this drug acts primarily on post P3 (response) processes (Naylor et al. 1985; Halliday et al. 1987). Few studies have used information processing paradigms that have assessed the effect of nicotine on P3 and RT. The findings of Edwards et al. (1985) are important and need to be replicated and extended to other experimental paradigms.

To address the above issues we examined the effects of a low dose of nicotine on multiple measures of information processing in a group of non-smokers. We assessed performance (RT, accuracy, and speed-accuracy trade-off measures) and the N1 and P3 components of the ERP. We assessed the N1 component, a negative voltage ERP with a peak latency of approximately 200 ms post-stimulus in the present task, because changes in P3 may reflect changes occurring earlier. N1 has been associated with early visual processes such as feature extraction or visual orienting (see, e.g., Luck et al. 1990). P3, a positive voltage component with a peak latency of 430 ms, has been associated with task relevant categorization of stimuli (see, e.g., Kutas et al. 1977). The functional distinction of these two components as evoked by our task is found in Brandeis et al. (1992). Speed-accuracy analyses were used because drugs may alter performance by improving speed but at the expense of decreasing accuracy. Recent findings suggest that speed-accuracy analyses may improve our theoretical understanding of drug effects on information processing (Wood and Jennings 1976; Servan-Schreiber et al. 1993). ERP components are determined by both latency and spatial distribution on the scalp. Many algorithms used to measure ERP latencies only use temporal information. In the present study, the latency and amplitude of the N1 and P3 were quantified using a validated mapping algorithm that uses both temporal and distributional information (Brandeis et al. 1992). We also assessed nicotine blood levels during the intervals when the subject performed the task. We hypothesized that low doses of nicotine would improve cognitive function by acting on attentional or stimulus processes. Specifically we hypothesized that nicotine would affect both RT and P3 latency.

Materials and methods

Subjects. Fifteen healthy non-smokers were recruited for this study. Subjects were selected who reported smoking less than five cigarettes in their lives. Blood cotinine levels were all below the detection limit of the assay (10 ng/ml), which confirmed at least subjects' recent (last 3–5 days) non-smoking status. Two subjects dropped out voluntarily, and one did not complete the nicotine session because of side effects (nausea and vomiting) from the subcutaneous nicotine injection. Complete data were obtained from 12 healthy young male adults, 21–33 years old (mean $\pm$ SD, 26.7 ± 3.7), with a level of education ranging from 2 to 5 years of college (3.5 ± 0.9), and weighing 62–83 kg (71 ± 6). Subjects were recruited by advertisement from a local university. They were given a thorough physical exam and gave their informed consent to participate in the study. They were paid $150 for completion of all sessions.

Procedure. Subjects were given an extensive practice session prior to the beginning of the experiment. They then came to the laboratory at 9 a.m. on three occasions, separated by at least 2 days. The first testing day was a control day, during which subjects were required to perform the task on the same time schedule as the two other sessions but without any injections or blood sampling. The remaining 2 days were randomly assigned to either placebo (0.8 ml SC saline) or nicotine (0.8 mg nicotine base in 0.8 ml saline). Drug testing was double-blind. Subcutaneous (SC) nicotine administration was chosen based on a preliminary clinical study showing that SC dosing results in blood levels of nicotine resembling those observed after smoking (Le Houezec et al. 1993). Injections were given in the deltoid area of the opposite arm from which blood samples were drawn. No restrictions on caffeine consumption were imposed. Subjects were instructed to consume their usual amounts of caffeine on all test days.

At 09:30, after administration of a subjective questionnaire and blood pressure and heart rate measurements, an intravenous

catheter was placed in the antecubital vein of one arm for blood sampling. A warmup on the task was given 30 min later. Testing started at 12:00 noon, consisting of a pre-injection test and two post-injection tests given at 15 and 45 min after SC injection. The 2 plus hours delay between insertion of the catheter and testing of nicotine effects was used to reduce the stressing effect of the catheter insertion.

Blood pressure, heart rate and a blood sample (5 ml) were then taken before and after each test. An 11-item subjective questionnaire was given five times (at −180, −45, +8, +35 and +65 min from the injection). Responses were given on a visual analog scale of 100 mm. For each item, the extreme left of the scale (0 mm) corresponded to "NOT AT ALL," while the right extremity (100 mm) corresponded to "EXTREMELY". Statements or questions were as follows: "I feel lightheaded or dizzy," "I feel high," "I feel nauseated," "I feel anxious or tense," "I feel stimulated," "My heart is beating faster," "I feel satisfied," "I feel alert and awake," "I feel calm and relaxed," "I am able to concentrate," and "How strong was the dose of the injection?" The last item was asked only after the injection, from the third to the fifth questionnaire.

Cognitive task. The choice RT task, called the Stimulus Evaluation-Response Selection (SERS) task (Callaway et al. 1985; Naylor et al. 1985) discriminates between two processing stages—stimulus evaluation and response selection—by independent manipulation of stimulus and response complexity. Increasing stimulus complexity increases RT and P3 latency. Increasing response complexity increases RT but has no effect on P3 latency. This task has been shown to be sensitive to many cholinergic, dopaminergic, and noradrenergic drugs (Callaway et al. 1985; Naylor et al. 1985; Halliday et al. 1987, 1989).

The subject was comfortably seated in a dimly lit sound-attenuated chamber, 144 cm from a computer screen. Stimuli were presented on the upper half of the screen through artificial 1 mm pupils in binoculars mounted on a combined head/chin rest. Artificial pupils were used to control for the effects of drugs on pupil size. There were two degrees of stimulus complexity (easy stimulus and hard stimulus) and two degrees of response complexity. The target was an "X" appearing on each trial in one of four horizontally arrayed positions. The target position varied randomly from trial to trial. In the easy stimulus condition the X appeared embedded with three dots in the three other positions. In the hard stimulus condition the X appeared embedded with three asterisks. Responses to stimuli presented on the screen were given on a four key keypad, held on the subject's lap. The response keys were horizontally arrayed, like the stimulus display. In the easy response condition, the subject depressed the right response key if the target appeared to the right, or the left response key if the target occurred to the left of the center of the display. The hard response condition required the subject to respond by pressing the button matching the exact spatial position of the X in the horizontal array. Eight blocks of 32 trials were presented during each test. Response complexity alternated from block to block beginning with the easy response condition. Within each block the stimulus condition varied randomly. This manipulation resulted in 64 trials each of the four possible conditions [Easy stimulus/Easy response (EE), Easy stimulus/Hard response (EH), Hard stimulus/Easy response (HE), and Hard stimulus/Hard response (HH)]. Prior to each trial a fixation display—a checkerboard pattern filling the four positions of the stimulus display—appeared on the screen. On each trial, the stimulus remained on the screen until the subject responded, to a maximum of 1852 ms, at which time the fixation display reappeared. The total fixed interval was 2100 ms with a jitter of 100 ms. After each block there was a pause, while the experimenter instructed the subject to switch to the alternate response condition. The entire test of 256 trials lasted 12–15 min. Thus, the time period of testing coincided with the expected time course of rising and falling concentrations of nicotine in the brain. Reaction time was measured from the onset of the stimulus to the onset of the response. Instructions emphasized speed and accuracy.

EEG recording. The EEG was recorded from 16 equidistant electrodes embedded in a cap. Sites of recording were Fz, Cz, Pz, Oz, A1, A2, T3, T4, T5, T6, C3, C4, P3, P4, and O1 and O2, which in the cap design were shifted laterally to be half-way between Oz and T5/T6. Fz was the recording reference and Fpz the ground. An electro-oculogram (EOG) was recorded between the outer canthus and above the eyebrow of the left eye. Trials for which the EOG peak-to-peak amplitude exceeded 50 μV were automatically excluded. Impedance of the electrodes was at or below 10 kOhm. The EEG was amplified by a Grass Model 12 polygraph, with filters set at 0.3–100 Hz bandpass. The sampling period was 800 ms (100 ms prestimulus to 700 ms post-stimulus), and the sampling rate was every 4 ms. Latency and amplitude of the P3 and N1 components of the ERP were identified by a topographic component algorithm that looks for the best fit between an ERP map series and a grand average template map. This method is fully described in Brandeis et al. (1992).

Chemical analyses. Blood was collected in tubes containing sodium heparin and was frozen until analysis. Plasma concentrations of nicotine, cotinine, and caffeine were measured by gas chromatography as described by Jacob et al. (1981), modified for use of a capillary column. The limit of quantification (as supported by quality control data) was 0.5 ng/ml for nicotine, 10.0 ng/ml for cotinine, and 50.0 ng/ml for caffeine.

Results

For RT and ERP measures we only report pre- versus post-1 (15 min) results, because results at post-2 (45 min) were not significant.

Performance effects

The most convincing demonstration that nicotine improved performance was found by examining speed-accuracy trade-off functions. Subjects can vary their reaction times by trading between accuracy or speed. When subjects are asked to respond quickly, they make a large number of errors. On the other hand, instructions to respond accurately result in an increase in mean reaction time. A plot of accuracy versus speed, termed a speed-accuracy function (SAF), can be approximated by a log function (Wood and Jennings 1976). When instructions stress speed, subjects' responses are moved to the left along the function. This represents a speeding of RT (increase in the number of fast RTs), but at the expense of increasing errors. Due to accuracy instructions in our task, subjects made few errors, so for individual subjects and task conditions there were not enough RTs clearly to delineate the fast/high error area of the SAF. In order to increase the number of RTs at this end of the distribution we removed the effects of individual differences and differences between task conditions. RTs were first normalized by task and subject. Normalized RTs were then grouped into equal sized bins. The normalized speed-accuracy function showed that fast RTs were accompanied by higher error rates than were slow RTs (i.e., subjects speeded their response but at the expense of increased errors).

Figure 1 shows the difference in post-1 minus pre-saline and post-1 minus pre-nicotine in the number of RTs for each bin. Nicotine increased the number of fast RTs relative to saline. Wilcoxon's signed rank test computed on the pre-post differences comparing saline with nicotine

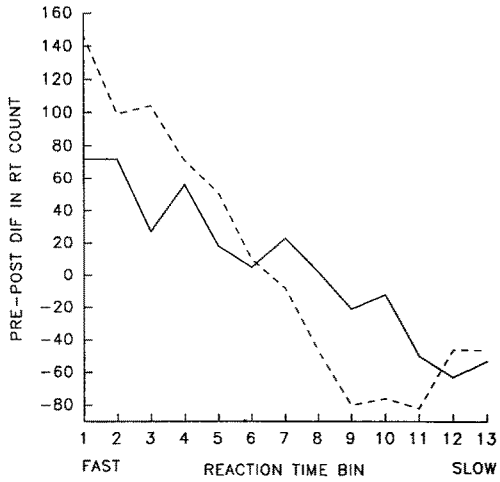

Fig. 1. Pre- minus post-test differences in the number of normalized RTs in each bin for saline and nicotine. ——— saline; – – – nicotine

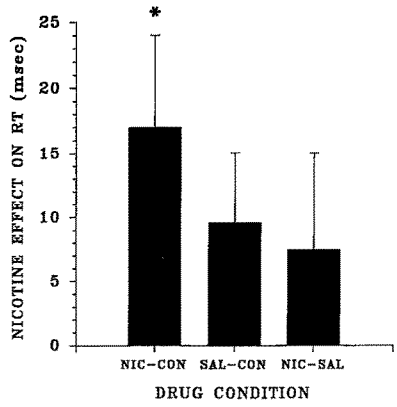

Fig. 2. Effects of nicotine on RT. Data represent difference between two drug conditions (e.g. nicotine-control) of the pre-post-1 difference. Positive values represent speeding of RT due to the first of the two named conditions; e.g. NIC-CON = (PRE-POST-1)NIC-(PRE-POST-1) CON

Table 1. Comparison of speed and accuracy by number of RTs (and proportion of errors) for the three fastest normalized RT bins

	Saline	Nicotine
Pre	556 (0.056)	649 (0.065)
Post	717 (0.089)	998 (0.067)

across all bins showed that this effect was significant ($W = 53$ $P < 0.04$). As Fig. 1 and Table 1 show, nicotine appears to increase the number of RTs in the fast end of the distribution. To confirm this impression we summed the number of responses in the three fastest bins. Nicotine reliably increased the number of RTs in these bins ($\chi^2 = 5.405$, $P < 0.05$). This effect was not accompanied by an increase in errors. Thus the increase in the number of fast RTs did not occur because subjects were trading speed for accuracy.

The effects of nicotine on mean reaction time (RT) and the latency and amplitude of N1 and P3 were analyzed with repeated measures ANOVA. Order of drug administration (Group) was a between subjects factor. Within subject factors included Drug (control, placebo, or nicotine), Time (pre-, post-1, or post-2), Stimulus level (easy or hard), and Response level (easy or hard). An overall analysis was conducted on all Drug and Time conditions, followed by specific 2 by 2 analyses (e.g., placebo versus nicotine and pre- versus post-1). Unless otherwise noted, significance levels were $P < 0.05$. For comparisons with more than 1 degree of freedom, P values were corrected with the Greenhouse-Geiser estimates of sphericity. The effect of drug was tested by the Drug by Time interaction.

The results for mean RT are illustrated in Fig. 2. Overall drug conditions analysis revealed a close to signifiicant Drug × Time interaction when comparing pre- to post-1 only [$F(2,20) = 3.22$, $P = 0.07$]. The figure shows the size of the saline and nicotine effects relative to the control day (positive indicates greater speeding in RT by nicotine or saline compared to the control day). Relative to saline or the control day, nicotine tended to speed RT.

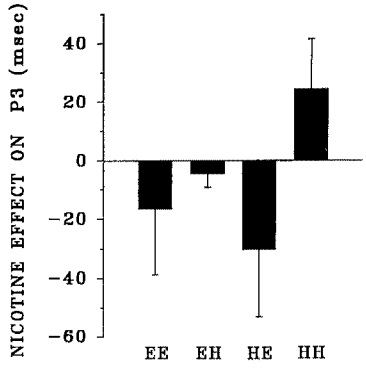

Fig. 3. Effects of nicotine on P3 latency by task condition. As in Fig. 2, data represent a double difference (PRE-POST-1)NIC-(PRE-POST-1) SAL. Task conditions: Easy stimulus/Easy response (EE); Easy stimulus/Hard response (EH); Hard stimulus/Easy response (HE); Hard stimulus/Hard response (HH)

This effect was significant only when nicotine was compared with the control day [$F(1,10) = 6.11$]. Neither nicotine compared with saline nor saline compared with the control day showed significant effects on RT [$F(1,10) = 3.58$, $P = 0.09$ and $F(1,10) = 0.89$, $P = 0.37$, respectively], although the speeding due to nicotine was still greater than the one due to saline. Order of drug administration had no effect.

N1 and P3 latency and amplitude

Statistical tests were computed on 11 subjects because one subject had noisy ERPs, probably due to excessive movements. No significant effects were found on N1 amplitude or latency.

Significant effects of nicotine on P3 latency were only found for the pre- to post-1 comparison. The main findings are summarized in Fig. 3. Relative to saline, nicotine speeded P3 latency by almost 25 ms in the Hard stimulus/Hard response condition, while slowing it in the Hard

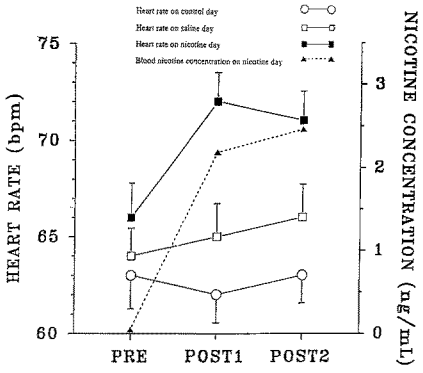

Fig. 4. Heart rate and plasma levels of nicotine in 12 non-smokers. Values are average of before and after each test (pre-, post-1, or post-2) ± SEM

stimulus/Easy response condition. The other task conditions were only slightly affected. The interaction involving nicotine and the task conditions (Drug by Time by Stimulus by Response) was significant [$F(1,9) = 10.42$]. Order of drug administration had no effect. There was no evidence from the ERP spatial distributions that P3 was contaminated by overlapping slow waves.

For P3 amplitude a significant Drug by Time interaction was found for the entire data set [$F(4,36) = 3.58$]. This effect was even more robust when comparing pre- to post-1 values [$F(2,18) = 6.88$]. The 2×2 analysis revealed a significant effect when comparing both nicotine with control [$F(1,9) = 7.35$] and saline with control [$F(1,9) = 9.41$], but not between saline and nicotine ($P = 0.26$). This effect was due to a post-injection increase in P3 amplitude during the two drug sessions compared with the control session.

Heart rate and plasma measures

Heart rate effects and plasma levels of nicotine are presented in Fig. 4. The average measurement before and after each test was used to compute levels in each of the three test conditions (pre-, post-1, and post-2). Statistical tests were conducted on 11 subjects because data for one subject were lost. The peak nicotine concentration was lower than that expected from a previous pharmacokinetic study in smokers (Le Houezec et al. 1993). Average peak level in the 12 non-smokers was 2.9 ± 0.6 ng/ml, while the same dose in smokers yielded a peak concentration of about 5–6 ng/ml. However, the heart rate response was substantial and clearly significant when comparing the pre-injection values to both post-injection values. A significant Drug by Time interaction was found for both overall drug conditions [$F(4,40) = 5.41$] and nicotine versus saline [$F(2,20) = 5.38$].

Questionnaires

Comparison between the first and second questionnaires of each session confirmed that neither Time nor Drug by Time effects due to the procedure (waiting from 9:30 to 12:00 with or without a catheter insertion) was responsible for further overall effects (all $P > 0.2$). Statistical analysis was then performed on the responses obtained in the last four questionnaires (those given before and after each test), except for the question: "how strong was the dose of the injection?", where only the three post-injection times were available. This question was only asked after placebo or nicotine injection. No subjective effects were significant except for the strength of the injection, which was clearly identified [$F(2,20) = 6.42$, for Drug by Time interaction].

Discussion

In this study low doses of nicotine given to non-smokers speeded information processing. This effect was best observed at the fast end of the RT distribution. However, nicotine did not cause subjects to trade speed for accuracy since it did not increase the number of errors. One has to postulate that nicotine affects some additional process that results in a different speed accuracy function. One possibility is that nicotine has a large effect on attention. Improvements in attention could maximize subjects' efforts, resulting both in faster and more accurate responses.

Nicotine also speeded mean RT relative to control and tended to speed it relative to saline. This effect was less dramatic than the speed-accuracy analysis, possibly because the increase in fast responses is not reflected in all the observations. It is of interest to note that a recent study using the same route of administration also reported a small non-significant speeding in mean RT with the same dose of nicotine (Jones et al. 1992). The fact that nicotine at these doses selectively acts on the fast end of the RT distribution may be a function of dose. We tested two smokers after various periods of deprivation using a 2.2-mg SC dose. Mean RT was speeded by 50 ms in both smokers.

Nicotine also speeded P3 latency in the most difficult task condition. This finding is consistent with results reported by other investigators. Herning and Pickworth (1985) examined the effects of nicotine gum (0, 4 and 8 mg doses) on P3 latency in an auditory oddball task and found it to be increased but only in the hardest task condition. These findings, like ours, suggest that nicotine might increase stimulus sensitivity when the task becomes more difficult. However, nicotine substantially slowed P3 latency in the HE condition and to some extent in the other task conditions. We have no explanation for this differential effect. However, it illustrates the importance of assessing nicotine effects on P3 latency for a wide variety of task conditions before implicating nicotine as affecting such broad constructs as stimulus evaluation processing.

The results of this study showed more interindividual variability than we anticipated. There appear to be two reasons for this variability. The first is that the dose may have been too small, although nicotine produced robust heart rate acceleration and subjective strength sensation. The nicotine levels in the non-smokers after 0.8 mg SC nicotine, as shown on Fig. 4, were all below the regression line obtained from a study in smokers (Le Houezec et al. 1993). Since non-smokers may experience nausea and

other side effects after doses of nicotine that are well tolerated by smokers, we chose a dose that we expected, from previous experiments, to be well tolerated and produce nicotine peak levels around 5 ng/ml. However, the non-smokers' blood nicotine levels peaked around 3 ng/ml. A possible explanation for that discrepancy is that non-smokers may have a larger apparent volume of distribution for nicotine. Nicotine has a great affinity for all kinds of tissues. In smokers, even in the morning when nicotine levels are very low, a certain amount of nicotine is stored in different tissues. This situation does not exist in non-smokers. Consequently, when nicotine is given to non-smokers, the apparent volume of distribution is larger, leading to smaller blood concentrations of nicotine. Thus the average effects on RT observed in the non-smokers may be small because the low dose used produced great individual differences that partially masked any consistent drug effect. This point illustrates the importance of assessing nicotine levels in studies that attempt to look at how nicotine affects performance.

The second reason for interindividual variability involves some possible effects due to the group order differences. Half of the subjects had saline for their first SC injection while the other half had nicotine. Two effects were observed. First, by chance the baseline RTs in one group were longer than in the other. Second, there appear to be differences depending on whether the subjects had nicotine or saline first. The subjects who had nicotine on the second session (the first session was always the control session) showed a smaller RT saline-nicotine difference than those who had nicotine on the third session. Since the subjects had limited experience with nicotine, and no experience with SC nicotine, in assigning subjects to the order group, we may have inadvertently produced differences in anxiety or expectancy concerning either how the injection or the nicotine would affect them. Since we provided some control for the effects of the injection, we have been able to show the importance of this procedure on RT and ERP results, particularly with the P3 amplitude measures that clearly show an effect of the injection itself, independently of drug condition. For these reasons, it might be important in the future that subjects experience the effects of the injection of nicotine and saline before testing the drug's effects on their cognitive behavior.

The speed-accuracy and P3 latency findings for the hardest task condition suggest that nicotine directly improves stimulus or attentional processing. The effect on P3 suggests that nicotine has cognitive, not simply motor effects. This interpretation is consistent with Warburtons' theory (Wesnes et al. 1983) that nicotine speeds the processing of visual information, leading to a more efficient stimulus encoding. However, the P3 findings for the other task conditions suggest that this interpretation may be too simple.

The nicotine results are also interesting when compared with other drugs. For example, a recent re-analysis of data from this same task showed that amphetamine increased the number of fast RTs (Servan-Schreiber et al. 1993). However, the effect is accompanied by an increase in errors suggesting that amphetamine moves subjects to the left of the same speed accuracy curve. Amphetamine only produces a small increase in P3. Nicotine on the other hand substantially increased P3 in the most difficult task condition. In this respect the actions of nicotine are more like those reported for anticholinergics like scopolamine (Callaway et al. 1985; Brandeis et al. 1992) except that scopolamine slows P3 in all task conditions.

The pharmacological and cognitive mechanisms underlying these effects are not known yet, but the comparisons suggest that nicotine may improve stimulus encoding while amphetamine affects response selection. The findings also suggest that the effects of low doses of nicotine can be detected when sophisticated measures of information processing are used. These methods may eventually be useful in providing a detailed understanding of the role played by information processing mechanisms in nicotine addiction.

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